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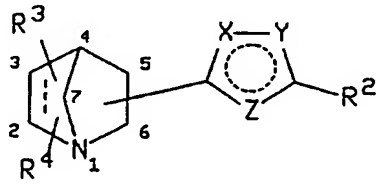
(54) Oxadiazolyl-azabicycloheptanes for the treatment of senile dementia.

(57) Oxadiazoles represented by structural formula I:



(I)

or a salt or prodrug thereof; wherein
one of X, Y or Z is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds);
R^2 represents a substituent of low lipophilicity;
the broken line represents an optional chemical bond; and
the substituents R^3 and R^4 may be present at any position, including the point of attachment to the oxadiazole ring, and R^3 represents halo, C_{1-4} alkoxy, carboxy, $-NR^7R^8$, C_{2-4} alkyl, C_{1-4} alkyl substituted with hydroxy or C_{1-4} alkoxy, or methyl or hydroxy in the 3-, 4- or 5-position; and R^4 represents hydrogen, halo, C_{1-4} alkoxy, hydroxy, carboxy, $-NR^7R^8$, C_{1-4} alkyl, or C_{1-4} alkyl substituted with hydroxy or C_{1-4} alkoxy; or R^3 and R^4 together represent carbonyl; and

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R^7 and R^8 independently represent hydrogen or C_{1-2} alkyl

are potent muscarinic agonists with good CNS penetrability, and are therefore useful in the treatment of neurological and mental illnesses; the compounds are also of benefit in the treatment of severe painful conditions. Processes for preparing these compounds are described, as also are pharmaceutical compositions containing them.

OXADIAZOLYL-AZABICYCLOHEPTANES FOR THE TREATMENT OF SENILE DEMENTIA

The present invention relates to a class of substituted oxadiazole compounds which stimulate central muscarinic acetylcholine receptors and therefore are useful in the treatment of neurological and mental illnesses whose clinical manifestations are due to cholinergic deficiency. Such diseases include presenile and senile dementia (also known as Alzheimer's disease and senile dementia of the Alzheimer type respectively), Huntington's chorea, tardive dyskinesia, hyperkinesia, mania and Tourette Syndrome. Alzheimer's disease, the most common dementing illness, is a slowly progressive neurological disorder characterised by marked deficits in cognitive functions including memory, attention, language and visual perception capabilities. The compounds of this invention are also useful analgesic agents and therefore useful in the treatment of severe painful conditions such as rheumatism, arthritis, and terminal illness.

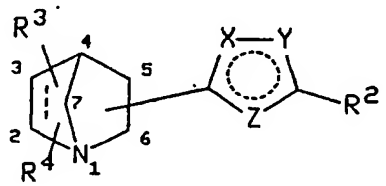
Compounds capable of enhancing muscarinic cholinergic transmission in the cortex should be beneficial in reversing the cholinergic deficiency in Alzheimer's disease and other diseases related to cholinergic dysfunction. However, most muscarinic agonists, including acetylcholine itself, are quaternary ammonium compounds incapable of penetrating the blood-brain barrier to any clinically significant extent following peripheral (e.g. oral) administration. Such agents fail to stimulate the desired central sites but instead induce undesired side-effects mediated exclusively by peripherally-located muscarinic acetylcholine receptors.

The oxadiazole compounds of the present invention are potent muscarinic agonists but, being tertiary amines with physiochemical properties (lipophilicity and pKa) consistent with CNS penetrability, can stimulate those central sites implicated in neurodegenerative disorders. It is believed that the enhancement of cholinergic transmission demonstrated by the compounds of this invention is achieved either directly by stimulating postsynaptic receptors, or indirectly by potentiating acetylcholine release.

EP-A-0261763, which was published on 30 March 1988, describes a class of compounds which includes oxadiazoles bearing a particular unsubstituted exo-1-azabicyclo[2.2.1]heptane substituent; these compounds are stated to be of potential use in the treatment and/or prophylaxis of dementia in mammals. This document does not, however, disclose exo-1-azabicyclo[2.2.1]heptane-substituted oxadiazoles in which the azabicyclic substituent is itself substituted.

In addition, EP-A-0239309, which was published on 30 September 1987, describes a class of oxadiazole compounds which are stated to be potent muscarinic agonists. These oxadiazoles are substituted on one of the ring carbon atoms thereof with a non-aromatic azacyclic or azabicyclic ring system; and substituted on the other ring carbon atom with a substituent of low lipophilicity. EP-A-0239309 specifically discloses 3-[5-(3-amino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptane; it will be noted, however, that the azabicyclic moiety of this latter compound is unsubstituted. Moreover, EP-A-0239309 generically discloses oxadiazoles in which the azabicyclic ring system is a 1-azabicyclo[2.2.1]heptane ring system optionally substituted with methyl or hydroxy. Nevertheless, none of the oxadiazole compounds specifically disclosed in EP-A-0239309 possesses a 1-azabicyclo[2.2.1]heptane substituent which is itself substituted.

The present invention provides an oxadiazole represented by structural formula I:



(I)

or a salt or prodrug thereof; wherein
one of X, Y or Z is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds);
R^2 represents a substituent of low lipophilicity;
the broken line represents an optional chemical bond; and
the substituents R^3 and R^4 may be present at any position, including the point of attachment to the oxadiazole ring, and R^3 represents halo, C_{1-4} alkoxy, carboxy, $-NR^7R^8$, C_{2-4} alkyl, C_{1-4} alkyl substituted

with hydroxy or C_{1-4} alkoxy, or methyl or hydroxy in the 3-, 4- or 5-position; and R^4 represents hydrogen, halo, C_{1-4} alkoxy, hydroxy, carboxy, $-NR^7R^8$, C_{1-4} alkyl, or C_{1-4} alkyl substituted with hydroxy or C_{1-4} alkoxy; or R^3 and R^4 together represent carbonyl; and

R^7 and R^8 independently represent hydrogen or C_{1-2} alkyl.

It will be appreciated that the nitrogen atom in the azabicycloheptane ring will carry a lone pair of electrons.

Preferably the oxadiazole ring is a 1,2,4-oxadiazole.

Suitably the group R^4 is hydrogen or methyl; and R^3 is C_{1-4} alkoxy, halo, $-NR^7R^8$, hydroxy(C_{1-4})alkyl or C_{1-4} alkoxymethyl, preferably methoxy, fluoro, amino, methoxymethyl or hydroxymethyl. Preferably R^4 is hydrogen.

The term "low lipophilicity" is intended to indicate that the group R^2 has a Rekker f value (hydrophobic fragment constant; see R. F. Rekker, "The Hydrophobic Fragmental Constant", Elsevier, 1977) of not greater than 1.5. For example, the methyl group has a value of 0.7 and the ethyl group a value of 1.26.

Thus the substituent of low lipophilicity represented by the group R^2 in formula I may be, for example, hydrogen, halogen, $-CF_3$, $-OR^7$, $-NR^7R^8$, $-NHOR^7$, $-NHNH_2$, $-CN$, $-CO_2R^7$, $-CONR^7R^8$, C_{2-5} alkenyl, C_{2-5} alkynyl, C_{1-2} alkyl, or C_{1-2} alkyl substituted with $-OR^7$, $-NR^7R^8$, $-SR^7$, $-CO_2R^7$, $-CONR^7R^8$ or halogen; wherein R^7 and R^8 are as defined with respect to formula I above.

Preferably the substituent of low lipophilicity is hydrogen, halogen, $-CF_3$, $-OR^7$, $-NR^7R^8$, $-NHNH_2$, $-CN$, $-CO_2R^7$, $-CONR^7R^8$, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-2} alkyl, or C_{1-2} alkyl substituted with $-OR^7$, $-NR^7R^8$, $-SR^7$, $-CO_2R^7$, $-CONR^7R^8$ or halogen. Particular values of R^2 are hydrogen, methyl, amino, dimethylamino, methoxycarbonyl and ethoxycarbonyl. A preferred group R^2 is amino.

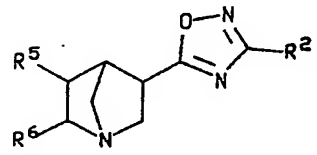
As used herein, the terms "alkyl" and "alkoxy" include straight chain alkyl and, where the alkyl group is of 3 or more carbons, branched chain alkyl and cycloalkyl. The terms "alkenyl" and "alkynyl" encompass both straight and branched chain. The term "halo" or "halogen" means fluoro, chloro or bromo.

One group of prodrugs of compounds of this invention have a substituent on the oxadiazole ring which is hydrolysable in vivo to an amino group.

Groups which are hydrolysable in vivo to an amino group on the compounds of this invention may be readily ascertained by administering the compound to a human or animal and detecting, by conventional analytical techniques, the presence of the corresponding compound having an amino substituent in the urine of a human or animal. Examples of such groups include, for example, amido and urethane substituents, in particular a group of formula -NH.Q, wherein Q represents CHO, COR or CO_2R, and R represents an optionally substituted hydrocarbon group.

In this context, the hydrocarbon group R includes groups having up to 20 carbon atoms, suitably up to 10 carbon atoms, conveniently up to 6 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, and aryl(C_{1-6}) alkyl. The alkyl group R may be straight or branched chain and may contain, for example, up to 12 carbon atoms, suitably from 1 to 6 carbon atoms. In particular the group may be substituted methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, n- or iso-heptyl, or n- or iso-octyl. Suitable cycloalkyl groups include cyclopentyl and cyclohexyl. The aryl group R includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, substituent groups.

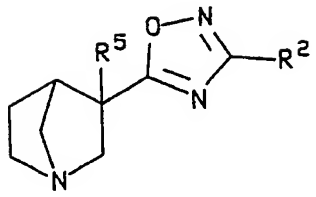
One sub-class of compounds within the scope of the present invention is represented by formula IIA:



(IIA)

wherein R^2 is as defined above, R^5 represents C_{1-4} alkyl, halo, $-NR^7R^8$, C_{1-4} alkoxy, hydroxy(C_{1-4})alkyl, C_{1-4} alkoxy(C_{1-4})alkyl or hydroxy, and R^6 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy; in particular wherein R^2 represents C_{1-2} alkyl, amino, dimethylamino or C_{1-3} alkoxycarbonyl, R^5 represents C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, fluoro, hydroxymethyl, methoxymethyl or amino, and R^6 represents hydrogen.

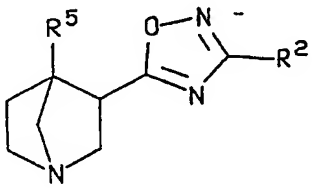
Another sub-class of compounds within the scope of this invention is represented by formula IIB:



(IIB)

wherein R^2 and R^5 are as defined with respect to formula IIA above; in particular wherein R^2 represents C_{1-3} alkyl and R^5 represents hydroxy.

A further sub-class of compounds within the scope of this invention is represented by formula IIC:



(IIC)

wherein R^2 and R^5 are as defined with respect to formula IIA above; in particular wherein R^2 and R^5 each represents C_{1-3} alkyl.

Specific compounds within the scope of the present invention include:
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-3-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-ethyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-6-methyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-amino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-fluoro-1-azabicyclo[2.2.1]heptane;
5-[5-(3-methyl-1,2,4-oxadiazol)-yl]-3-methoxymethyl-1-azabicyclo[2.2.1]heptane;
5-[5-(3-methyl-1,2,4-oxadiazol)-yl]-3-methyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-hydroxymethyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-methoxy-1-azabicyclo[2.2.1]heptane;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-methyl-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-amino-1-azabicyclo[2.2.1]heptane;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-4-methyl-1-azabicyclo[2.2.1]heptane;
and salts and prodrugs thereof.

The compounds of this invention all have more than one asymmetric centre, and can therefore exist as both enantiomers and diastereoisomers. In particular, they can exist as exo and endo isomers. It is to be understood that the invention covers all such isomers and mixtures thereof.

Also included within the scope of the present invention are salts of the novel compounds. It will be appreciated that salts of the compounds for use in medicine will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of the invention or their non-toxic pharmaceutically acceptable salts. Acid addition salts, for example, may be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Where the novel compound carries a carboxylic acid group the invention also contemplates salts thereof, preferably non-toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium or calcium salts thereof.

Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group. Such quaternary ammonium derivatives penetrate poorly into the central nervous system and are therefore useful as peripherally selective muscarinic agents,

agents to reduce gastric acid secretion, agents to block the muscarinic actions of acetylcholinesterase inhibitors in the treatment of myasthenia gravis and as agents to co-administer with muscarinic agonists in Alzheimer's disease.

It is believed that those compounds of the invention which directly stimulate post-synaptic receptors are particularly useful as analgesic agents.

The method of treatment of this invention includes a method of treating Alzheimer's disease, senile dementia of the Alzheimer type, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania or Tourette syndrome by the administration to a patient in need of such treatment of an effective amount of one or more of the novel compounds.

The invention further provides a method of treating severe painful conditions (e.g. rheumatism, arthritis and terminal illness) which comprises administering to a patient in need of analgesic treatment an effective amount of one or more of the novel compounds.

This invention therefore also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier.

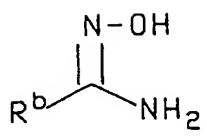
It may, where appropriate, be advantageous, in order to reduce unwanted peripherally mediated side-effects, to incorporate into the composition a peripherally acting cholinergic antagonist (or anti-muscarinic agent). Thus the compounds of the invention may advantageously be administered together with a peripheral cholinergic antagonist such as N-methylscopolamine, N-methylatropine, propantheline, methantheline or glycopyrrolate.

The compounds of the invention can be administered orally, parenterally or rectally at a daily dose of about 0.01 to 10 mg/kg of body weight, preferably about 0.1 to 1 mg/kg, and may be administered on a regimen of 1-4 times a day. When a cholinergic antagonist is administered, it is incorporated at its conventional dose.

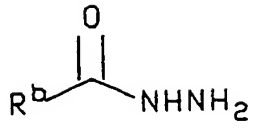
The pharmaceutical formulations of this invention preferably are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tabletting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil and peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspension include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone and gelatin.

The compounds of this invention may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of formula R^a-CO_2H with either a compound of formula IIIA or a compound of formula IIIB or a salt thereof:



(IIIA)

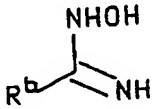


(IIIB)

wherein one of R^a and R^b is a substituted 1-azabicyclo[2.2.1]heptane ring, and the other is a group of low lipophilicity.

Suitable reactive derivatives of the acid R^a-CO_2H include esters, for example C_{1-4} alkyl esters; thioesters, for example pyridylthioesters; acid anhydrides, for example $(R^aCO)_2O$; acid halides, for example acid chlorides; orthoesters; and primary, secondary and tertiary amides.

When the compound of formula IIIA is employed the product of the reaction is a 1,2,4-oxadiazole. It will be appreciated that the compound IIIA can also be considered as the alternative tautomeric form:



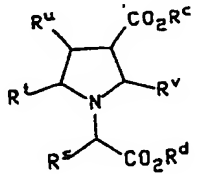
A 3-substituted 1,2,4-oxadiazol-5-yl compound is produced if R^a represents the azabicycloheptane group and R^b in formula IIIA represents the substituent of low lipophilicity. In this case, a preferred reactive derivative of the acid R^aCO_2H is a C_{1-4} alkyl ester. The reaction is conveniently carried out in tetrahydrofuran, dimethylformamide or a lower alkanol such as ethanol, propanol or isopropanol at about 20° to 100° C for about 1 to 6 hours.

A 5-substituted 1,2,4-oxadiazol-3-yl compound is produced by the process of this invention when R^a represents the substituent of low lipophilicity and R^b represents the azabicycloheptane group. For this reaction a suitable reactive derivative is the acid chloride or the acid anhydride $(R^aCO)_2O$. The reaction may be carried out by treating compound IIIA, in the cold, e.g. from about -5° to +10° C, with the reactive derivative, followed by heating at about 80° to 120° C for about 1 to 6 hours.

When the compound of formula IIIB is employed, the product of the process of this invention is a 1,3,4-oxadiazole. In this case, a preferred reactive derivative of the acid R^aCO_2H is an orthoester of formula $R^aC(OR^g)_3$ where R^g represents C_{1-3} alkyl. The process is conveniently effected by heating the hydrazide IIIB with the orthoester in a solvent such as methanol at reflux temperature for about 2 to 8 hours. An intermediate of formula $R^b.CO.NH.N=C(R^a)OR^g$ may be isolated by evaporation of the solvent. The intermediate is then treated with a strong base such as potassium t-butoxide or 1,8-diazabicyclo[5.4.0]-undec-7-ene in butanol for about 10 to 24 hours at about 90° to 150° C.

After the above process is complete, one substituent of low lipophilicity can be converted to another. For example an amino group may be converted to chloro, or hydrazo, $-NHNH_2$, via the intermediacy of diazonium, $-N_2^+$. Similarly, a chloro substituent may be converted to methoxy by reaction with a nucleophile such as methoxide; and alkoxycarbonyl groups may be converted, via carboxy, to an amino substituent, $-NH_2$.

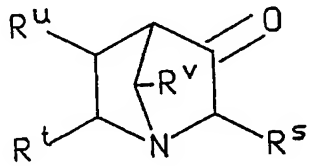
The reactive derivatives of the compound R^aCO_2H may, for example, be prepared by cyclisation of a compound of formula IV:



(IV)

wherein R^s, R^t, R^u and R^v represent hydrogen, carboxylic acid ester, or a substituent R^3 or R^4 as defined above, or a group which is convertible thereto; at least one of R^s, R^t, R^u and R^v being other than hydrogen: and

R^c and R^d are hydrocarbon groups, in particular C_{1-5} alkyl, such as methyl or ethyl; to produce a compound of formula V:



(V)

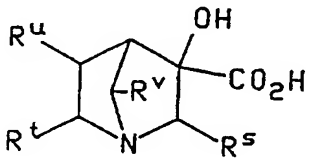
or a ketal thereof; and optionally converting the carbonyl group in compound V or the ketal thereof, or any of the groups R^s, R^t, R^u and R^v, to a substituent group R^3 or R^4 or to a $-CO_2H$ group or reactive derivative thereof.

The intermediate of formula V is a novel compound and forms a further aspect of this invention. It provides a valuable route to substituted 1-azabicyclo[2.2.1]heptanes used in the process of the present invention.

The cyclisation of compound IV is carried out in the presence of a strong base, such as potassium t-butoxide, followed by acidification, for example by concentrated hydrochloric acid. This reaction causes the condensation of the groups CO_2R^a and CO_2R^b. When one of the groups R^s, R^t, R^u and R^v represents an ester group, this reaction will liberate the free acid. For ease of isolation it is preferable to esterify the acid in situ, for example by treatment with methanol and hydrochloric acid.

The carboxylic acid group and thence its reactive derivative, which is employed to react with the oxadiazole moiety, may be generated from any of the substituent groups R^s, R^t, R^u or R^v initially present in compound IV. In this way, by selection of one such group as an ester group, the point of attachment to the oxadiazole can be determined.

Alternatively the ketone group which is generated in the intermediate V may be converted to a carboxylic acid group, for example by reaction with an alkali metal cyanide such as sodium cyanide, to produce a compound VI:



(VI)

The hydroxy group in compound VI may then be converted to a group R^3 or R^4 to produce a substituent at the same position as the point of attachment to the oxadiazole ring.

In any of the above reactions it may be necessary and/or desirable to protect any sensitive groups in the compounds. For example, if R^a and/or R^b include amino, carboxy, hydroxy or thiol groups, these may be protected in conventional manner. Thus, suitable protecting groups for hydroxy groups include silyl groups such as trimethylsilyl or t-butyldimethylsilyl, and etherifying groups such as tetrahydropyranyl: and for amino groups include benzyloxycarbonyl and t-butyloxycarbonyl. Carboxy groups are preferably protected in a reduced form such as in the form of their corresponding protected alcohols, which may be subsequently oxidised to give the desired carboxy group. Thiol groups may be protected by disulphide formation, either with the thiol itself or with another thiol to form a mixed disulphide. The protecting groups may be removed at any convenient stage in the synthesis of the desired compound according to conventional techniques.

The following Examples illustrate the preparation of compounds according to the invention. Each of the

compounds of the Examples demonstrates an affinity for the muscarinic receptor, having an IC_{50} - (concentration required to displace 50% of specific [^{3}H]-N-methylscopolamine binding from rat cortical membrane preparations) significantly lower than 100μM. Agonist behaviour and penetrability into the central nervous system of the compounds of the Examples were assessed in a rat behavioural model by measuring the ability of the compound under test to elicit a mouth movement response and/or a hypothermic response characteristic of centrally-active muscarinic agonists (see Salamone et al., Psychopharm., 1986, 88, 467). In this model, the compounds of all the Examples were active at doses of 10 mg/kg or less.

In the Examples, all temperatures are in °C; THF is tetrahydrofuran; and ether is diethyl ether.

EXAMPLE 1

exo - 3[5-(3-Methyl-1,2,4-oxadiazol)yl]-1-azabicyclo [2.2.1]heptan-3-ol hydrochloride

(a) 1-Benzyl-3-carbomethoxypyrrolidine

This was prepared from 1-benzyl-3-carbomethoxy-5-pyrrolidinone by the procedure described by Kornet et al, J. Org. Chem., 1968, 33 3637.

(b) 1-Methoxycarbonylmethyl-3-methoxycarbonylpyrrolidine.

A solution of 1-benzyl-3-carbomethoxypyrrolidine (50g, 228 mmol) in methanol (300 ml) was subjected to hydrogenolysis over $Pd(OH)_2$ (6g) on a Parr shaker for 7 hours. The suspension was filtered through celite and the solvent removed under vacuum to give 3-carbomethoxypyrrolidine (30 g) as a clear liquid. This amine (29 g, 225 mmol) was added to a rapidly stirred suspension of potassium carbonate (64 g) in xylene (350 ml) at 130° C. After 0.25 hours a solution of methylbromoacetate (35 g, 230 mmol) in xylene (100 ml) was added dropwise and the mixture heated under reflux for 2 hours. The xylene solution was decanted from the inorganic residue which was taken up into water (200 ml) and extracted with dichloromethane (3 x 250 ml).

The combined organics were dried (sodium sulphate) and evaporated to afford the title compound (43 g) as a yellow liquid, δ (60MHz $CDCl_3$) 2.10 - 3.30 (7H, m, 3 x CH_2 and 1 x CH); 3.37 (2H, s, CH_2 - CO_2Me) and 3.72 (6H, s, 2 x CO_2Me).

(c) 1-Azabicyclo[2.2.1]heptan-3-one

A solution of 1-methoxycarbonylmethyl-3-methoxycarbonylpyrrolidine (5g, 24.9 mmol) in toluene (75 ml) was added dropwise, over a 3 hour period, to a rapidly stirred solution of potassium-t-butoxide (8 g, 71 mmol) in toluene (250 ml) at 130° C. The mixture was heated under reflux for 4 hours, cooled to room temperature, and concentrated hydrochloric acid (75 ml) added dropwise and stirred for 0.25 hour. The separated toluene solution was extracted with concentrated hydrochloric acid (3 x 50 ml) and the combined aqueous extracts heated under reflux for 16 hours. The solvent was reduced to half volume under vacuum, basified to PH > 10 with potassium carbonate and extracted with chloroform (6 x 100 mls). The material isolated from the organic extracts was chromatographed on silica in dichloro methane-methanol (90 : 10) to give 1-azabicyclo-[2.2.1]heptan-3-one (1.2 g) as a yellow oil, δ (360 MHz, $CDCl_3$) 1.75-1.80 (1H, m, 0.5 x CH_2); 2.06-2.12 (1H, m. 0.5 x CH_2); 2.70-2.81 (4H, m, 2 x CH_2-N), and 3.00-3.12 (3H, m, CH_2-N and CH).

(d) exo-3-Carbomethoxy-1-azabicyclo[2.2.1]heptan-3-ol

The hydrochloride salt of 1-azabicyclo[2.2.1]heptan-3-one was prepared by addition of ethereal hydrogen chloride to a solution of the compound in methanol. A solution of sodium cyanide(0.7 g, 14.3 mmol) in water (4 ml) was added dropwise to a solution of 1-azabicyclo-[2.2.1]heptan-3-one hydrochloride (1.7 g, 11.5 mmol) in water (5 ml) at -5° C. The mixture was stirred at 0° C tor 1 hour and the precipitated

cyanohydrin filtered and washed with cold water The solid was taken up into concentrated hydrochloric acid (15 ml) and stirred for 24 hours at room temperature. The residue obtained after removal of the solvent and drying was dissolved in a saturated solution of hydrogen chloride in methanol (100 ml) and stirred at room temperature for 16 hours. The solvent was removed under vacuo. the residue taken up into water (25 ml), basified to pH 10 with potassium carbonate and extracted with dichloromethane (8 x 50 ml). The combined extracts were dried and evaporated to give the title compound (1.3 g), m/e 171 (M^+); δ (360 MHz, $CDCl_3$) 1.39-1.48 (1H, m, 0.5 x CH_2); 2.16-2.21 (1H, m, 0.5 x CH_2); 2.40-2.50 (2H, m, CH_2-N); 2.66-2.72 (2H, m, CH and 0.5 x CH_2-N); 3.22-3.26 (1H, m, 0.5 x CH_2-N); 3.83 (3H, s, CO_2me).

(e) exo-3[5-(3-Methyl-1,2,4-oxadiazol)yl]-1-azabicyclo [2.2.1]heptan-3-ol hydrochloride.

Activated molecular sieves (Type 4A, 0.5 g) were added to a stirred solution of acetamide oxime (0.4 g, 5.4 mmol) in anhydrous tetrahydrofuran (50 ml) under nitrogen. After 0.5 hour, sodium hydride (0.14 g of a 80% dispersion in oil, 4.6 mmol) was added and the solution stirred for a further 0.5 hour. A solution of exo-3-carbomethoxy-1-azabicyclo[2.2.1]heptan-3-ol (0.4 g, 2.34 mmol) in tetrahydrofuran (20 ml) was then added and the mixture stirred under reflux for 2 hours. The mixture was cooled to room temperature, quenched with water (20 ml) and extracted with dichloromethane (5 x 100 ml). The combined extracts were dried (sodium sulphate) the solvent evaporated and the residue chromatographed through alumina using dichloromethane-methanol (95 : 5) as eluant to give the title oxadiazole (0.2 g) as a crystalline solid. The product was further purified as the hydrochloride salt, m.p. 225-227° C (isopropanol): (Found C, 46.33; H, 6.07; N, 17.81 $C_9H_{13}N_3O_2$.HCl requires C, 46.65; H, 6.05; N,18.14%; m/e 195 (M^+ for free base); δ (360 MHz, $CDCl_3$) 1.46-1.56 (1H, m, 0.5 x CH_2); 2.12-2.24 (1H, m, 0.5 x CH_2); 2.45 (3H, s, Me); 3.26-3.34 (1H, m, 0.5 x CH_2-N); 3.35 (1H, d, J = 4.75 Hz, CH-bridge-head); 3.44-3.60 (2H, m, 2 x 0.5 x CH_2-N); 3.75 (1H, dd, J = 2.8 and 13 Hz, 0.5 x CH_2-N); 3.88-3.90 (1H, m, 0.5 x CH_2N); 4.1 (1H, dd, J = 2.48 and 13 Hz, 0.5 x CH_2-N).

EXAMPLE 2

3[5-(3-Methyl-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-ols

(a) trans-3,4-Dicarbomethoxypyrrolidine

This was prepared from glycine by the procedure reported by Joucla et al. (J. Chem. Soc., Chem. Commun, 1985, 1566).

(b) 1-Methoxycarbonylmethyl-trans-3,4-dicarbo methoxypyrrolidine

A solution of trans-3,4-dicarbomethoxypyrrolidine (4.1 g, 22 mmol) in xylene (30 ml) was added to a rapidly stirred suspension of potassium carbonate (7 g) in xylene (150 ml) at 120° C. After 0.25 hours a solution of methylbromoacetate (3.45 g, 22.5 mmol) in xylene (30 ml) was added dropwise and the mixture stirred and heated under reflux for 2 hours. The solution was then decanted from the inorganic residue which was taken up into water (100 ml) and extracted with dichloromethane (3 x 150 ml). The combined organics were dried (sodium sulphate) and evaporated to afford the title compound as a yellow liquid (6 g); δ (360 MHz, $CDCl_3$) 2.96-3.11 (4H, m, 2 x CH_2-N); 3.34 (2H, ABq, J = 16.5Hz, CH_2-CO_2me); 3.46-3.52 (2H, m, 2 x CH) and 3.74 (9H, s, 3 x CO_2me).

(c) 3-Carbomethoxy-5,5-dimethoxy-1-azabicyclo [2.2.1]-heptane

A solution of 1-methoxycarbonylmethyl-trans-3,4-dicarbomethoxypyrrolidine (5 g, 19.31 mmol) in toluene (75 ml) was added dropwise over a 3 hour period, to a rapidly stirred solution of potassium t-butoxide (9 g, 80 mmol) in toluene (250 ml) at 130° C. The mixture was heated under reflux for 4 hours,

cooled to room temperature, and concentrated hydrochloric acid (75 ml) added dropwise and stirred for 0.25 hour. The separated organic phase was extracted with concentrated hydrochloric acid (3 x 50 ml) and the combined aqueous extracts heated under reflux for 16 hours. The solvent was removed in vacuo, the residue dried and taken up into a saturated solution of hydrogen chloride in methanol (150 ml). The mixture was stirred at room temperature for 24 hours, the solvent removed in vacuo, water (50 ml) added and basified to PH>10 with potassium carbonate. The solution was extracted with dichloromethane (5 x 150 ml) and the combined extracts dried (sodium sulphate) and evaporated. The residue was purified by chromatography on silica-gel in dichloromethane-methanol (93 : 7) to give the title azanorborane as a yellow liquid (0.5 g), and as a single isomer δ (360 MHz, $CDCl_3$) 2.44 (1H, dd, J = 9.8, 3Hz, 0.5 x CH_2); 2.63 (1H, dd, J = 12.7, 3Hz, 0.5 x CH_2; 2.77 (1H, d, J = 12.7Hz, 0.5 x CH_2); 2.80-3.10 (5H, m, 2 x CH and 1.5 x CH_2); 3.11 (3H, s, OMe); 3.24 (3H, s, OMe); 3.71 (3H,s,CO_2Me).

(d) 3[5-(3-Methyl-1,2,4-oxadiazol)yl]-5,5-dimethoxy-1-azabicyclo[2.2.1]-heptane.

Activated molecular series (Type 4A, 1 g) were added to a stirred solution of acetamide oxime (0.6 g, 8.1 mmol) in anhydrous tetrahydrofuran (50 ml) under nitrogen. After 0.5 hour, sodium hydride (0.2 g of a 80% dispersion in oil, 6.7 mmol) was added and the solution stirred for a further 0.5 hour. A solution of exo-3-carbomethoxy-5,5-dimethoxy-1-azabicyclo[2.2.1]-heptane (0.5 g, 2.3 mmol) in tetrahydrofuran (20 ml) was then added and the mixture heated at reflux for 6 hours. The mixture was cooled to room temperature diluted with water (15 ml) and extracted with dichloromethane (5 x 100 ml). The combined extracts were dried (sodium sulphate), the solvent evaporated and the residue chromatographed through silica-gel using dichloro-methane-methanol (95:5) as eluant to afford a clear oil (0.26 g), δ (360 MHz, $CDCl_3$) 2.38 (3H, s, Me); 2.43 (1H, dd, J = 12.7, 3 Hz, 0.5 x CH_2); 2.73 (1H, dd, J = 10, 3.2 Hz, 0.5 x CH_2); 2.95 (1H, d, J = 12.8 Hz 0.5 x CH_2); 2.99 (1H, s, CH); 3.10 (1H, d, J = 12.8 Hz, 0.5 x CH_2); 3.07-3.22 (2H, m, CH_2); 3.22 (3H, s, O Me); 3.27(3H, s, O Me); 3.47-3.50 (1H, m, CH).

(e) 3[5-(3-Methyl-1,2,4-oxadiazol)yl]-1-aza bicyclo[2.2.1]-heptan-5-one.

A solution of 3[5-(3-methyl-1,2,4-oxadiazol)yl]-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane (0.26 g, 1.26 mmol) in perchloric acid (2.5 ml) was stirred at 85 °C for 16 hours. The mixture was diluted with water (10 ml), neutralised with sodium carbonate and extracted with dichloromethane (4 x 50 ml). The combined extracts were dried (sodium sulphate) and evaporated and the residue chromatographed on silica-gel using dichloromethane-methanol (93 : 7) as eluant to give the title ketone as a mixture of two isomers (0.2 g), δ - (360 MHz, $CDCl_3$), 2.35 and 2.39 (3H, s, Me); 2.89-3.94 (8H, m 3 x CH_2 and 2 x CH).

(f) 3[5-(3-Methyl-1,2,4-oxadiazol)yl]-1-azabicyclo-[2.2.1]heptan-5-ols

Sodium borohydride (30 mg, 0.8 mmol) was added to a solution of 3-[5(3-methyl-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-one (0.2 g, 1 mmol) in ethanol (20 ml), at 0 °C. The mixture was stirred at 0 °C for 0.5 hour and then at room temperature for 0.5 hour. Excess borohydride was destroyed by addition of 2M hydrochloric acid and the solvent removed under reduced pressure. The residue was taken up into water (10 ml) and basified to pH 10 with potassium carbonate. Extraction with dichloromethane (5 x 50 ml), drying (sodium sulphate) and evaporation of solvent gave a crude product which was chromatographed through silica-gel using dichloromethane-methanol (90:10) to afford two separated components in a ratio of 3:1. The less polar, major isomer, Isomer A, was isolated as a white crystalline solid, m.p. 136-139 °C (isopropylalcohol-ether). (Found C, 55.02; H, 6.69; N, 21.16. $C_9H_{13}N_3O_2$ requires C, 55.37, H, 6.71, N, 21.52%); δ (360 MHz, $CDCl_3$) 2.17 (1H, dt, J = 3.6, 13 Hz, 0.5 x CH_2); 2.38 (3H, s, CH_3); 2.68 (1H, broad d, J = 10 Hz, 0.5 x CH_2); 2.79 (1H, dd, J = 3.6, 10 Hz, 0.5 x CH_2; 2.95 (1H, d, J = 4.4 Hz, -CH); 3.11-3.22 (3H, m, 0.5 x CH_2 and CH_2); 3.88 (1H, dd, J = 6.4 Hz, -CH-oxadiazole); 4.50-4.55 (1H, m, -CH-OH).

The more polar isomer, Isomer B, was isolated as a crystalline solid, m.p. 171 -174 °C (isopropylacoholether δ (360 MHz, $CDCl_3$) 2.30 (1H, dt, J = 3.8, 13 Hz, 0.5 x CH_2); 2.37 (3H, s, CH_3); 2.68 (1H, dd, J = 3.5, 10 Hz, 0.5 x CH_2); 2.75 (1H, dd, J = 2.5, 10 Hz, 0.5 x CH_2); 3.17-3.31 (3H, m) and 3.41-3.52 (2H, m, -CH-oxadiazole, -CH-bridgehead, 0.5 x CH_2 and CH_2); 4.49-4.55 (1H, m, -CH-OH).

EXAMPLE 3

Exo-3-[5-(3-Amino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-ol

a) 3-[5-(3-Amino-1,2,4-oxadiazol)yl]-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane.

Sodium (0.75 g, 32.6 mmol) was cut into small pieces and added to a stirred mixture of hydroxyguanidine sulphate (2.47 g, 9.30 mmol) in methanol (60 ml, predried over molecular sieves). After 0.25 h a solution of 3-carbomethoxy-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane (1 g, 4.65 mmol) in methanol (5 ml) was added and heated at 80° C for 2 h.
The reaction mixture was decanted from the molecular sieves, the solvent removed under vacuum and the residue taken up into water (10 ml). Extraction into dichloromethane (4 x 100 ml), drying (Na_2SO_4), and removal of solvent under vacuum, was followeu by chromatography through alumina (Grade II/III) using dichloromethane/methanol (98:2), as eluant, to afford the title amino oxadiazole (0.26 g); m/e 240 ($M^{\bullet}$)$^{\bullet}$, 225 ($^{\bullet}M-CH_3$); δ (360 MHz, $CDCl_3$) 2.41 (1H, dd, J = 13 Hz and 3.2 Hz, CH of CH_2); 2.73 (1H, dd, J = 10 Hz and 3.3 Hz, CH of CH_2); 2.91 - 3.19 (5H, m, 2 x CH_2 and CH); 3.21 (3H, s, OMe); 3.26 (3H, s, OMe); 3.35 - 3.68 (1H, m, CH-oxadiazole); 4.36 (2H, brs, NH_2).

b) 3-[5-(3-Amino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-one.

A solution of 3-[5-(3-amino-1,2,4-oxadiazol)yl-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane (0.26 g, 1.08 mmol) in perchloric acid (4 ml) was stirred at 85° C for 24 h. The mixture was diluted with water (10 ml), neutralised with sodium carbonate and extracted with dichloromethane (4 x 100 ml). The combined extracts were dried (Na_2SO_4), the solvent evaporated, and the residue washed with cold dichloromethane (50ml) to give the title ketone (0.14 g); δ (360 MHz, d_6-DMSO) 2.72 - 3.33 (7H, m, 3 x CH_2 and CH); 3.40 (1H, dd, J = 8 Hz and 5 Hz, CH-oxadiazole); 6.27 (2H, brs, NH_2);

c) Exo-3-[5-(3-Amino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-ol

Sodium borohydride (36 mg, 0.94 mmol) was added to a solution of 3-[5-(3-amino-1,2,4-oxadiazol)yl-1-azabicyclo[2.2.1]heptan-5-one (0.14 g, 0.72 mmol) in ethanol (40 ml), at 0° C. The mixture was stirred at 0° C for 0.5 h and at room temperature for 0.5 h. Excess borohydride was destroyed by addition of 2N hydrochloric acid and the solvent removed under reduced pressure. The residue was taken up into water (10 ml), basified to pH 10 with potassium carbonate, and extracted with dichloromethane (4 x 100ml). Drying (Na_2SO_4) and removal of solvents under vacuum, were followed by chromatography of the residue through alumina (Grade II/III) using dichloromethane/methanol (90:10) as eluant to give exo- 3-[5-(3-amino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]-heptan-5-ol (20 mg), m.p. 220 - 221.5° C (ethanol); [Found: C, 49.39; H, 6.36; N, 27.64. $C_8H_{12}N_4O_2$. 0.15 EtOH requires C, 49.08; H, 6.40; N, 27.58%); m/e 196 ($M^{\bullet}$); δ(360 MHz D_2O) 2.15 (1H, d, J = 11 Hz, CH of CH_2); 2.72 (2H, brs, CH_2-N); 3.03 (1H, d, J = 4.4 Hz,CH-bridgehead); 3.04 - 3.21 (3H, m, 2 x CH_2); 3.65 - 3.72 (1H, m, CH-oxadiazole); 4.50 - 4.55 (1H, m, CH-OH).

EXAMPLE 4

Exo-3-[5-(3-methyl-1,2,4-oxadiazoi)yl]-5-fluoro-1-azabicyclo[2.2.1]heptane Hydrochloride

Diethylaminosulphur trifluroride (0.21 g, 1.30 mmol) was added dropwise to a solution of exo-3-[5-(3-methyl-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-ol (0.25 g, 1.28 mmol) in dichloromethane (30 ml), at -78° C, and stirred at this temperature for 1 h before allowing to warm to room temperature and stir for 1.5 h. Water (20 ml) was added and basified with potassium carbonate. Extraction into dichloromethane (3 x 100 ml), drying (Na_2SO_4) and removal of solvents under vacuum was followed by chromatography through

silica-gel, using dichioromethane/methanol (90:10) as eluant, to give a crude product. Further chromatography through alumina using dichloromethane/methanol (99:1) as eluant gave the title fluoride (50 mg). The hydrochloride salt was prepared, m.p. 197 - 200°C (isopropylalchol/ether); [Found: C, 45.98; H, 5.60; N, 17.58. $C_9H_{12}N_3FO$. $HCl.O.1H_2O$ requires C, 45.90; H, 5.61; N, 17.58%]; δ(360 MHz, $CDCl_3$) 2.36 (3H, s, CH_3); 2.50 - 3.10 (8H, m, 3 x CH_2 and 2 x CH); 4.67 (1H, d, J_{H-F} = 56 Hz, CH-F).

EXAMPLE 5

Exo-5-[(3-Methyl-1,2,4-oxadiazol)yl]-3-methoxymethyl-1-azabicyclo[2.2.1]heptane Sesquioxalate

a) 3-Hydroxymethyl-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane

A solution of 3-carbomethoxy-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane (4.19 g, 19.5 mmol) in anhydrous THF (40 ml) was added dropwise, with stirring, to a solution of lithium aluminium hydride (19.5 ml of 1M solution in THF, 19.5 mmol), in THF (50 ml), at 5°C. Stirring at 5°C for 1 h was followed by stirring at room temperature for 1 h. Water (3 ml) and 2N sodium hydroxide (1 ml) were added and the reaction mixture filtered through hyflo filter aid. The filter pad was washed with dichloromethane (200 ml), the combined organics dried (Na_2SO_4), and evaporated to give 3-hydroxymethyl-5,5-dimethoxy-1-azabicyclo-[2.2.1]heptane, (2,83 g) m.p. 151 - 153°C (ethylacetate); [Found: C, 57.54, H, 9.04; N, 7.30. $C_9H_{17}NO_3$ requires C, 57.73; H, 9.15; N, 7.48%]; δ(360 MHz, $CDCl_3$) 2.20 - 2.27 (1H, m, CH of CH_2); 2.38 (1H, dd, J = 9 Hz and 2.4 Hz, CH of CH_2); 2.39 - 2.45 (1H, m, CH of CH_2); 2.48 (1H, dd, J = 13 Hz and 3.2 Hz, CH of CH_2); 2.78 (1H, d, J = 4.0 Hz, CH-bridgehead); 2.87 (1H, dd, J = 13 Hz and 1.7 Hz, CH of CH_2); 2.95 (1H, dd, J = 9.6 Hz and 2.3 Hz, CH of CH_2); 3.02 - 3.09 (1H, m, CH); 3.24 (3H, s, OMe); 3.26 (3H, s, OMe); 3.65 - 3.82 (2H, m, CH_2-OH).

b) 3-Methoxymethyl-1-azabicyclo[2.2.1]heptan-5-one

Diethylaminosulphurtrifluoride (0.69 g, 4.3 mmol) was added dropwise to a stirred solution of 3-hydroxymethyl-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane (0.80 g, 4.3 mmol) in dichloromethane (40 ml), at -78°C. After 1 h the reaction mixture was warmed to room temperature and stirred for 16 h. Water (10 ml) and dichloromethane (100 ml) were added and the aqueous basified with potassium carbonate. Extraction into dichloromethane (3 x 100 ml), drying (Na_2SO_4) and evaporation of solvent were followed by chromatography of the residue through silica-gel using dichloromethane/methanol (93:7) as eluant to give the title ketone (0.23 g) as an orange oil; δ(360 MHz, $CDCl_3$) 2.38 - 2.46 (1H, m, CH of CH_2); 2.64 - 3.02 (6H, m, 2 x CH_2, CH of CH_2 and CH-bridgehead); 3.30 (3H, s, OMe); 3.26 - 3.66 (3H, m, CH_2-OMe and CH).

c) 5-(1,3-Dithian-2-ylidene)-3-methoxymethyl-1-azabicyclo[2.2.1]heptane

n-Butylithium (2.03 ml of 1.6M solution in hexane, 3.25 mmol) was added to a solution of 2-trimethylsilyl-1,3-propanedithiane (0.68 g, 3.54 mmol) in anhydrous THF (50 ml), at -35°C, and the solution stirred for 2 h. A solution of 3-methoxymethyl-1-azabicyclo[2.2.1]heptan-5-one (0.42 g 2.71 mmol) in THF (5 ml) was added and the reaction mixture warmed to room temperature and stirred for 1 h. Water (6 ml) was added followed by dichloromethane (100 ml) and stirred for 0.1 h. Chromatography of the residue remaining after extraction into dichloromethane (3 x 100 ml), drying (Na_2SO_4) and evaporation of solvent, through silica gel, using dichloromethane/methanol (91:9) as eluant, gave 5-(1,3-dithian-2-ylidene)-3-methoxymethyl-1-azabicyclo[2.2.1]heptane (0.53 g); m/e 157 (M^+);δ(360 MHz, $CDCl_3$) 1.96 - 2.20 (4H, m, 2 x CH_2); 2.30 - 3.20 (10H, m, 4 x CH_2 and 2 x CH); 3.32 (3H, s, OMe); 3.40 - 3.54 (2H, m, CH_2-OMe).

d) 5-Carbomethoxy-3-methoxymethyl-1-azabicyclo[2.2.1]heptane

The preceeding dithioketene acetal (0.53 g, 2.06 mmol) was dissolved in methanol (saturated with hydrogen chloride) (45 ml) and stirred at 55°C for 24 h. The solvent was removed under vacuum, the residue taken up into water (6 ml) and basified with potassium carbonate. The aqueous was extracted into dichloromethane (4 x 70 ml), dried (Na_2SO_4) and the solvents removed under vacuum. The resultant residue was purified by chromatography through alumina (Grade II/III) using dichloromethane/methanol (99:1) as eluant to give the title ester (0.26 g) as an orange oil, m/e 199 (M^+); δ(360 MHz, $CDCl_3$) 1.92 - 1.98 (1H, m, CH); 2.29 - 2.86 (5H, m, 2 x CH_2 and CH); 2.87 (1H, d, J = 4 Hz, CH-bridgehead); 2.95 - 3.08 (2H, m, CH_2); 3.35 (3H, s, OMe); 3.29-3.42 (2H, m, CH_2-OMe); 3.68 (3H, s, CO_2Me).

e) Exo-5-[5-(3-methyl-1,2,4-oxadiazol)yl]-3-methoxy methyl-1-azabicyclo[2.2.1]heptane Sesquioxalate

Sodium hydride (78.4 mg of an 80% dispersion in oil, 2.61 mmol) was added to a stirred solution of methylamide oxime (0.22 g, 2.90 mmol) in anhydrous THF (70 ml) in the presence of molecular sieves (1 g). The reaction mixture was stirred at 75°C for 0.25 h before adding a solution of 5-carbomethoxy-3-methoxymethyl-1-azabicyclo[2.2.1]heptane (0.26 g, 1.31 mmol) in THF (5 ml) and refluxing for 1.5 h. The reaction mixture was cooled to room temperature and water (15 ml) and dichloromethane (100 ml) added. The aqueous was extracted with dichloromethane (4 x 100 ml), the combined extracts dried (Na_2SO_4), and evaporated, and the residue chromatographed through alumina, using dichloromethane/methanol (99:1) as eluant to give the title oxadiazole. The compound was further purified as the sesquioxalate salt, m.p. 122.5 - 124.5°C (dichloromethane/ether); [Found: C, 46.65; H, 5.67; N, 11.14. $C_{11}H_{17}N_3O_2.1.6(CO_2H)_2$ requires C, 46.41; H, 5.56; N, 11.44%]; δ(360 MHz, D_2O) 2.38 (3H, s, Me); 2.75 - 3.10 (2H, m, CH_2); 3.20 - 3.30 (2H, m, 2 x CH); 3.40 (3H, s, OMe); 3.53 - 3.91 (6H, m, 3 x CH_2); 3.90 - 3.96)1H, m, CH-oxadiazole).

EXAMPLE 6

exo-5-[5-(3-methyl-1,2,4-oxadiazol)yl]-3-methyl-1-azabicyclo[2.2.1]heptane Hydrochloride

a) 3-Methyl-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane

n Butyllithium (2.21ml of a 2.5M solution in hexane, 5.53 mmol) was added to a solution of 3-hydroxymethyl-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane (0.94 g, 5.03 mmol) in THF (50 ml), at 0°C, and stirred for 1 h. Tetramethylphosphoramidic chloride (1.53 ml, 10.05 mmol) was added to the reaction mixture and stirred at room temperature for 1.5 h. Removal of the solvent under vacuum was followed by chromatography through alumina using dichloromethane/methanol (99:1) as eluant to give the desired 3-tetramethylphosphoramidate (1.4 g), δ(360 MHz, $CDCl_3$) 2.25 - 2.73 (6H, m, 2 x CH_2 and 2 x CH); 2.62 (6H, s, NMe); 2.66 (6H, s, NMe); 2.89 - 3.00 (1H, m, 0 5 x CH_2); 3.18 (6H, s, OMe); 3.20 - 3.27 (1H, m, 0.5 x CH_2); 4.05 - 4.30 (2H, m, CH_2-O).

Lithium metal (0.31 g, 43.6 mmol) was added to freshly distilled ethylamine (50 ml) and stirred at 0°C until the metal had dissolved. A solution of t-butylalcohol (0.97 g, 13.1 mmol) and the preceding phosphoramidate (1.4 g, 4.36 mmol), in anhydrous THF (10 ml) was added to the reaction mixture at such a rate so as to maintain the blue colouration. After stirring for 0.5 h the reaction was quenched by cautious addition of water (50 ml), extracted into dichloromethane (4 x 100 ml), dried (Na_2SO_4) and the solvent evaporated. Chromatography through alumina (Grade II/III) eluting with dichloromethane/methanol (97.5:2.5) gave 3-methyl-5,5 dimethoxy-1-azabicyclo[2.2.1]heptane (0.55 g) as a colourless oil; m/e 171 (M^+); δ(360 MHz, $CDCl_3$) 1.30 (3H, d, J = 7.3 Hz, MeCH); 1.98 - 2.04 (1H, m, CH); 2.37 (1H, dd, J = 12.5 Hz and 3.3 Hz, 0.5 x CH_2); 2.43 (1H, dd, J = 9.3 Hz and 3.7 Hz, 0.5 x CH_2); 2.49 (1H, d, J = 3.7 Hz, CH-bridgehead); 2.63 - 2.70 (2H, m, CH_2); 2.91 (1H, dd, J = 9.4 Hz and 2 Hz, 0.5 x CH_2); 2.95 (1H, d, J = 11 Hz, 0.5 x CH_2); 3.18 (3H, s, OMe); 3.20 (3H, s, OMe).

b) 3-Methyl-1-azabicyclo[2.2.1]heptan-5-one

A solution of 3-methyl-5,5-dimethoxy-1-axabicyclo[2.2.1]heptane (0.55 g, 3.22 mmol) in perchloric acid (3 ml) was stirred for 1h at room temperature. Dichloromethane (40 ml) was added followed by water (10 ml) and the aqueous basified with sodium carbonate. The aqueous was extracted with dichloromethane (4 x 40 ml), the combined extracts dried (Na_2SO_4) and the solvent removed under vacuum to give the title ketone (0.35 g), m/e 125 (M^+) δ(360 MHz, $CDCl_3$) 1.05 (3H, d, J = 7 Hz, Me-CH); 2.13 - 2.18 (1H, m, CH); 2.60 - 2.70 (2H, m, CH and 0.5 x CH_2); 2.74 (1H, dd, J = 17.5 and 4.3 Hz, 0.5 x CH_2); 2.87 (1H, dd, J = 10.4 and 4.3 Hz, 0.5 x CH_2); 3.03 (1H, dd, J = 10.4 and 2.6 Hz, 0.5 x CH_2); 3.09 (1H, d, J = 17.5 Hz, 0.5 x CH_2) 3.33 - 3.39 (1H, m, 0.5 x CH_2).

c) 3-Methyl-5-(1,3-dithian-2-ylidene)-1-azabicyclo[2.2.1]heptane

This was prepared by the procedure described for Example 5 part c. Thus a solution of 3-methyl-1-azabicyclo[2.2.1]heptan-5-one (0.35 g, 2.80 mmol) in THF when treated with 2-trimethylsilyl-2-lithio-1,3-propane dithiane gave the title product (0.44 g), after chromatography through alumina, using dichloromethane/methanol (97:3) as eluant; m/e 227 (M^+); δ(360 MHz, $CDCl_3$) 0.96 (3H, d, J = 7 Hz, Me-CH) 2.12 - 2.70 (4H, m, 1.5 x CH_2 and CH); 2.50 - 3.50 (10H, m, CH and 4.5 x CH_2).

d) 3-Methyl-5-carbomethoxy-1-azabicyclo[2.2.1]heptane

This was prepared by the procedure described for Example 5 part d. Thus treating the preceeding dithioketene acetal (0.44 g, 4.41 mmol) with methanol (saturated with hydrogen chloride) (30 ml) gave, after alumina chromatography, eluting with dichloromethane, the title ester (0.14 g) as a pale yellow liquid m/e 169 (M^+), δ(360 MHz, $CDCl_3$) 0.93 (3H, d, J = 7 Hz, Me-CH); 1.75 - 1.80 (2H, m, CH and 0.5 x CH_2); 2.48 - 3.06 (7H, m, 2 x CH and 2.5 x CH_2); 3.68 (3H, s, Me).

e) exo-5-[5-(3-Methyl-1,2,4-oxadiazol)yl]-3-methyl-1-azabicyclo[2.2.1]heptane Hydrochloride

This was prepared by the procedure described for Example 5 part e. Thus 3-methyl-5-carbomethoxy-1-azabicyclo[2.2.1]heptane (0.14 g, 0.83 mmol) gave the title oxadiazole (40 mg) after chromatography through silica-gel using dichloromethane/methanol (93:7) as eluant and upon treatment with ethereal hydrogen chloride, m.p. 175-177°C, (isopropyl alcohol); [Found: C, 51.81; H, 6.99; N, 17.73. $C_{10}H_{15}N_3O.HCl.0.15\ H_2O$ requires C, 51.68; H, 7.02; N, 18.09%]; m/e 193 (M^+ free base); δ(360 MHz, $CDCl_3$) 1.25 (3H, d, J = 6.7 Hz, Me-CH); 2.41 (3H, s, Me); 2.75 - 2.84 (2H, m, CH and 0.5 x CH_2); 3.24 (1H, bd, J = 3.5 Hz, CH-bridgehead); 3.42 (1H, d, J = 10 Hz, 0.5 x CH_2); 3.46 (1H, d, J = 10 Hz, 0.5 x CH_2); 3.70 - 3.88 (3H, m, CH_2 and 0.5 x CH_2); 4.04 (1H, dd, J = 8.5 and 5.5 Hz, CH-oxadiazole).

EXAMPLE 7

exo-3-[5-(3-Methyl-1,2,4-oxadiazol)yl]-5-hydroxy methyl-1-azabicyclo[2.2.1]heptane Hydrochloride

a) 3-[5-(3-Methyl-1,2,4-oxadiazol)yl]-5-(1,3-Dithian-2-ylidene)-1-azabicyclo[2.2.1]heptane

This was prepared from 3 [5-(3-methyl-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-one (1.21 g, 6.27 mmol) by the procedure described for Example 5 part c. The product (1.37 g) was obtained as an orange oil, m/e 295 (M^+); δ(360 MHz, $CDCl_3$) 2.13 - 2.31 (2H, m, CH_2); 2.38 (3H, s, Me); 2.70 - 3.50 (12H, m, 5 x CH_2 and 2 x CH).

b) 3-[5-(3-Methyl-1,2,4-oxadiazolyl)yl]-5-carbomethoxy-1-azabicyclo[2.2.1]heptane

This was prepared from the preceding dithioketene acetal (1.37 g, 4.84 mmol) by the procedure described for Example 5 part d. The product (0.8 g) was obtained as a yellow oil; m/e 237 (M^+); δ(360 MHz, $CDCl_3$) 2.37 (3H, s, Me); 2.70 - 3.40 (9H, m, 3 x CH_2 and 3 x CH); 3.70 (3H, s, CO_2Me).

c) exo-3-[5-(3-Methyl-1,2,4-oxadiazolyl)yl]-5-hydroxymethyl-1-azabicyclo[2.2.1]heptane Hydrochloride

A solution of 3-[5-(3-methyl-1,2,4-oxadiazolyl)yl]-5-carboxymethoxy-1-azabicyclo[2.2.1]heptane (0.80 g, 3.38 mmol) in anhydrous THF (10 ml) was added dropwise to a stirred solution of diisobutylaluminium hydride (8.44 ml of a 1.0M solution in toluene 8.44 mmol), in THF (50 ml), at -70°C. Stirring at -70°C for 0.25 h was followed by warming to room temperature and stirring for 0.5 h. Aqueous workup, extraction into dichloromethane (5 x 50 ml), drying (Na_2SO_4) and removal of the solvent under vacuum gave the crude product which was purified by chromatography through alumina using dichloromethane/methanol (97:3) as eluant. The product (0.52 g) was obtained on a colourless oil. The hydrochloride salt was prepared. [Found: C, 48.52; H, 5.93; N, 16.83; $C_{10}H_{15}N_3O_2.HCl$ requires C, 48.88; H, 6.11; N, 17.11%]; m/e 209 (M^+-free base);; δ(360 MHz, $CDCl_3$); 1.90 (1H, brs, OH). 2.37 (3H, s, Me); 2.38 - 3.20 (9H, m, 3 x CH_2 and 3 x 0.5); 3.50 - 3.69 (2H, m, CH_2-OH).

EXAMPLE 8

exo-3-[5-(3-Methyl-1,2,4-oxadiazol)yl]-4-methyl-1-azabicyclo[2.2.1]heptane. Hydrochloride and endo-3-[5-(3-methyl-1,2,4-oxadiazol)yl-4-methyl-1-azabicyclo[2.2.1]heptane Hydrochloride

a) 4-Methyl-1-azabicyclo[2.2.1]heptan-3-one

A solution of 1-carbomethoxymethyl-3-methyl-3-carbomethoxypyrrolidine (14g, 65mmol) in toluene (150ml) was added over a 0.75h period to a rapidly stirred solution of potassium-t-butoxide (24g, 21mmol) in toluene (750ml), at 140°C for 4h, cooled to room temperature and concentrated hydrochloric acid (250ml) added. The aqueous was separated and the organic extracted with 3 further portions of hydrochloric acid (3 x 150ml). The combined aqueous was heated at 110°C for 8h, the water removed to half the volume, basified with potassium carbonate, and extracted with dichloromethane (4 x 250ml). The combined extracts were dried (Na_2SO_4), evaporated, and the residue chromatographed through alumina, using dichloromethane/methanol (98:2) as eluant to give the title ketone (4g) as a colourless oil. The product was characterised as the hydrochloride salt, m.p. 243-245°C (isopropylalcohol), [Found, C, 51.87; H, 7.24; N, 8.68. $C_7H_{11}NO.HCl$ requires C, 52.02; H, 7.48; N, 8.67%); m/e 126 $(M+H)^+$; δ (360MHz, $CDCl_3$) 1.35 (3H, s, Me); 1.98-2.06 (1H, m, CH of CH_2); 2.29-2.38 (1H, m, CH of CH_2); 3.18-3.62 (3H, m, CH_2 and CH of CH_2); 3.79-3.92 (2H, m, CH_2); 4.06 (1H, dd, J = 2.7 and 17Hz, CH of CH_2).

b) 3-(1,3-Dithian-2-ylidene)-4-methyl-1-azabicyclo[2.2.1]heptane

n-Butyllithium (20ml of a 1.6M solution in hexane, 32.2mmol) was added to a stirred solution of 2-trimethylsilyl-1,3-dithiane (4.69g, 24.3mmol) in anhydrous THF (150ml), at -50°C. After 2h, a solution of 4-methyl-1-azabicyclo[2.2.1]heptan-3-one (2.54g, 20mmol) in THF (10ml) was added and the reaction mixture warmed to room temperature. Aqueous work up and extraction into dichloromethane gave the crude product which was chromatographed through silica gel using dichloromethane/methanol (93:7) as eluant to give the title compound (1.06g) as a low melting solid, m.p. 48-49°C, m/e 227 (M^+); δ (360MHz, $CDCl_3$) 1.64 (3H, s, Me); 1.64-1.91 (2H, m, CH_2); 2.08-2.15 (2H, m, CH_2); 2.38 (1H, dd, J = 3.45 and 9.2 Hz, CH of CH_2); 2.58-3.20 (7H, m, 3 of CH_2 and CH of CH_2); 3.24 (1H, dd, J = 3.5 and 16Hz, CH of CH_2); 3.57 (1H, d, J = 16Hz, CH of CH_2).

c) 3-Carbomethoxy-4-methyl-1-azabicyclo[2.2.1]heptane

The preceding dithioketeneacetal (1.7g, 7.5mmol) was dissolved in methanol (saturated with hydrogen-chloride, 100ml) and stirred at 65°C for 4h. The solvent was removed under vacuum, water (20ml) added and basified to pH10 with potassium carbonate. The aqueous was extracted into dichloromethane (4 x 150ml), dried (Na_2SO_4) and the residue remaining after removal of solvents under vacuum chromatographed through alumina, using dichloromethane/methanol (99:1) as eluant, to give the title ester (0.82g) as a pale yellow oil; δ (360MHz, $CDCl_3$) 1.22 (3H, s, Me); 1.23-1.27 (1H, m, CH of CH_2); 1.43-1.52 (1H, m, CH of CH_2); 2.12-2.15 (1H, m, CH of CH_2); 2.23-2.26 (1H, m, CH of CH_2); 2.72-2.82 (2H, m, CH_2); 2.93-3.07 (2H, m, CH_2); 3.16-3.21 (1H, m, CH of CH_2); 3.68 (3H, s, CO_2Me).

d) exo-3-[5-(3-Methyl-1,2,4-oxadiazol)yl]-4-methyl-1-azabicyclo[2.2.1]heptane. Hydrochloride and endo-3-[5-(3-methyl-1,2,4-oxadiazol)yl]-4-methyl-1-azabicyclo[2.2.1]heptane. Hydrochloride

Sodium hydride (0.36g of an 80% dispersion in oil, 12.1mmol) was added to a stirred solution of methylamide oxime in THF (50ml), in the presence of molecular sieves (4A) and the reaction mixture heated at 70°C for 0.25h. A solution of 3-carbomethoxy-4-methyl-1-azabicyclo[2.2.1]heptane (0.82g, 4.85mmol) in THF (15ml) was then added and heated at 70°C for 1.5h. Water (15ml was added followed by dichloromethane (150ml) and the aqueous separated and extracted with dichloromethane (4 x 75ml). The combined extracts were dried (Na_2SO_4) and evaporated, and the residue chromatographed through alumina using dichloromethane/methanol (100-99:1) as eluant to give the title compounds. The mixture of products was further chromatographed through silica-gel using dichloromethane/methanol (95:5) as eluant to give 2 separated components.

The less polar compound was identified as the exo isomer (0.29g) and was further purified as the hydrochloride salt, m.p. 226-227°C (isopropylalcohol); (Found: C, 52.15; H, 6.89; N, 18.08. $C_{10}H_{15}N_3O.HCl$ requires C, 52.29; H, 7.02; N, 18.29%); δ (360MHz, D_2O) 1.13 (3H, s, Me); 2.09-2.18 (2H, m, CH_2); 2.42 (3H, s, Me); 3.23 (1H, d, J = 10Hz, CH of CH_2); 3.45-3.52 (2H, m, CH_2); 3.62-3.70 (1H, m, CH of CH_2); 3.75-3.79 (1H, m, CH of CH_2); 3.82-3.89 (1H, m, CH of CH_2); 3.91-3.97 (1H, m, CH-oxadiazole).

The more polar compound was identified as the second title compound and was characterised as the hydrochloride salt, m.p. 196-197°C (isopropyl alcohol); (Found: C, 51.51: H, 7.18; N, 17.96. $C_{10}H_{15}N_3O.HCl.0.2H_2O$ requires C, 51.48; H, 7.09; N, 18.01%); δ (360MHz, D_2O) 1.50 (3H, s, Me); 1.67-1.76 (1H, m, CH of CH_2); 1.86-1.95 (1H, m, CH of CH_2); 2.43 (3H, s, Me); 3.35 (1H, dd, J = 2.5 and 9.2Hz, CH of CH_2); 3.45-3.53 (2H, m, CH_2); 3.62-3.67 (1H, m, CH of CH_2); 3.80-3.84 (1H, m, CH-oxadiazole); 3.91-4.06 (2H, m, CH_2).

EXAMPLE 9

exo-3-[5-(3-Dimethylamino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-ol

a) exo-3-[5-(3-Dimethylamino-1,2,4-oxadiazol)yl]-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane

exo-3-[5-(3-Dimethylamino-1,2,4-oxadiazol)yl]-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane was prepared from 3-carbomethoxy-5,5-dimethoxy-1-azabicyclo[2.2.1]heptane (2.73g, 13mmol) and dimethyl hydroxy guanidine hydrochloride (4.35g, 31mmol) by the procedure described for Example 2 part d. The crude product was chromatographed through silica gel, eluting with dichloromethane/methanol (95:5) to give the title dimethylamino oxadiazole as a low melting solid (2.94g), δ (250MHz, $CDCl_3$) 2.40 (1H, dd, J = 3 and 18Hz, CH of CH_2); 2.75 (1H, dd, J = 3 and 10Hz, CH of CH_2); 2.93 (1H, d, J = 18Hz, CH of CH_2); 2.96 (1H, s, bridgehead-H); 2.97 (1H, d, J = 13Hz, CH of CH_2); 2.99 (6H, s, NMe); 3.04-3.15 (2H, m, CH_2); 3.21 (3H, s, OMe); 3.26 (3H, s, OMe); 3.32-3.37 (1H, m, CH-oxadiazole).

b) exo-3-[5-(3-Dimethylamino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-one

Deketalisation of the preceding ketal (0.5g, 1.87mmol) was achieved using perchloric acid 17ml) using the procedure described for Example 2 part e. The crude product was chromatographed through silica- gel using dichloromethane/methanol (95:5) as eluant to give the title ketone (0.37g): δ (250MHz, $CDCl_3$) 2.88 (1H, dd, J = 4.1 and 17.9Hz, CH of CH_2); 3.00 (6H, s, NMe); 3.09-3.46 (7H, m, 2 of CH_2, CH of CH_2 CH-oxadiazole, and CH-bridgehead).

c) exo-3-[5-(3-Dimethylamino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-ol

Sodium borohydride (0.035g, 0.92mmol) was added to a solution of the preceding ketone (0.11g, 0.046mmol) in ethanol (10ml), at 0° C, and stirred for 0.20h. The reaction mixture was warmed to room temperature, stirred for 0.1h, sodium methoxide (0.2g, 3.7mmol) added, and the solution stirred for 1.5h. The solvent was removed under vacuum, water (20ml) added and extracted with ethyl acetate (5 x 50ml). The combined extracts were dried (Na_2SO_4) and evaporated to give the crude product which was recrystallised from ethyl acetate, to give the title compound (55mg) as a white crystalline solid, m.p. 149-150° C; δ (360MHz, $CDCl_3$) 1.88 (1H, brs, OH); 2.12-2.17 (1H, m, CH of CH_2); 2.63 (1H, d, J = 10.3Hz, CH of CH_2); 2.81 (1H, dd, J = 3.5 and 10.3Hz, CH of CH_2); 2.91 (1H, d, J = 4.1Hz, CH-bridgehead); 3.00 (6H, s, NMe); 3.07-3.25 (3H, m, CH_2 and CH of CH_2); 3.74 (1H, dd, J = 5.3 and 8.3Hz, CH-oxadiazole); 4.47-4.52 (1H, m, CH-OH).

EXAMPLE 10

exo-3-[5-(3-Dimethylamino-1,2,4-oxadiazol)yl-5-methyl-1-azabicyclo[2.2.1]heptan-5-ol

Methylmagnesium bromide (0.32ml of a 3M solution in ether, 0.96mmol) was added to a stirred solution of exo-3-[5-(3-dimethylamino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-one (0.175g, 0.79mmol) in ether (3ml), at 0° C. The reaction mixture was warmed to room temperature stirred for 2h, water (20ml) then added and extracted with dichloromethane (4 x 25ml). The combined extracts were dried (Na_2SO_4) and evaporated to give the title alcohol (0.10g) m.p. 143-147° C; δ (250MHz, $CDCl_3$) 1.45 (3H, s, Me); 1.70 (1H, br s, OH); 2.43 (1H, dd, J = 3 and 12.7Hz, CH of CH_2); 2.67 (1H, br s, CH-bridgehead); 2.73-2.81 (3H, m, CH_2 and CH of CH_2); 2.99 (6H, s, NMe); 3.04-3.30 (2H, m, CH_2); 3.87 (1H, dd, J = 4.2 and 12.4Hz, CH-oxadiazole).

EXAMPLE 11

Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0 mg, respectively, of the following compounds are prepared as illustrated below:

exo-3-[5-(3-Methyl-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-ol.
exo-3-[5-(3-Methyl-1,2,4-oxadiazol)yl]-5-fluoro-1-azabicyclo[2.2.1]heptane. Hydrochloride.
exo-5-[5-(3-Methyl-1,2,4-oxadiazol)yl]-3-methyl-1-azabicyclo[2.2.1]heptane. Hydrochloride.
exo-3-[5-(3-Methyl-1,2,4-oxadiazol)yl]-4-methyl-1-azabicyclo[2.2.1]heptane. Hydrochloride.
exo-3-[5-(3-Dimethylamino-1,2,4-oxadiazol)yl]-1-azabicyclo[2.2.1]heptan-5-ol.

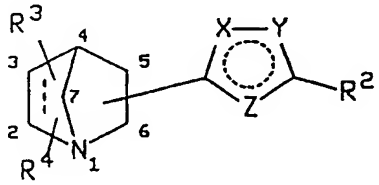
TABLE FOR DOSES CONTAINING FROM 1-25 MG OF THE ACTIVE COMPOUND			
	Amount-mg		
Active Compound	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

TABLE FOR DOSES CONTAINING FROM 26-100 MG OF THE ACTIVE COMPOUND			
	Amount-mg		
Active Compound	26.0	50.0	100.0
Microcrystalline Cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

All of the active compound, lactose, and a portion of the corn starch are mixed and granulated to a 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0 mg, 2.0 mg, 25.0 mg, 26.00 mg, 50.0 mg and 100.0 mg of active ingredient per tablet.

Claims

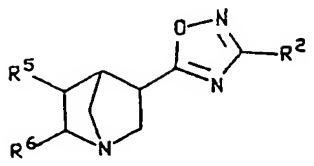
1. An oxadiazole represented by structural formula I:



(I)

or a salt or prodrug thereof; wherein
one of X, Y or Z is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds);
R^2 represents a substituent of low lipophilicity;
the broken line represents an optional chemical bond; and
the substituents R^3 and R^4 may be present at any position, including the point of attachment to the oxadiazole ring, and R^3 represents halo, C_{1-4} alkoxy, carboxy, $-NR^7R^8$, C_{2-4} alkyl, C_{1-4} alkyl substituted with hydroxy or C_{1-4} alkoxy, or methyl or hydroxy in the 3-, 4- or 5-position; and R^4 represents hydrogen, halo, C_{1-4} alkoxy, hydroxy, carboxy, $-NR^7R^8$, C_{1-4} alkyl, or C_{1-4} alkyl substituted with hydroxy or C_{1-4} alkoxy; or R^3 and R^4 together represent carbonyl; and
R^7 and R^8 independently represent hydrogen or C_{1-2} alkyl.

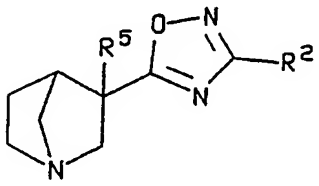
2. An oxadiazole as claimed in claim 1 represented by formula IIA:



(IIA)

wherein R^2 is as defined in claim 1, R^5 represents C_{1-4} alkyl, halo, $-NR^7R^8$, C_{1-4} alkoxy, hydroxy(C_{1-4})-alkyl, C_{1-4} alkoxy(C_{1-4})alkyl or hydroxy, and R^6 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy.

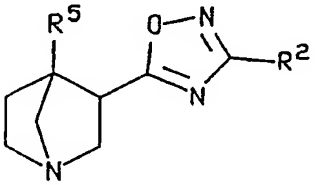
3. An oxadiazole as claimed in claim 1 represented by formula IIB:



(IIB)

wherein R^2 is as defined in claim 1 and R^5 is as defined in claim 2.

4. An oxadiazole as claimed in claim 1 represented by formula IIC:



(IIC)

wherein R^2 is as defined in claim 1 and R^5 is as defined in claim 2.

5. A compound as claimed in claim 1 selected from the following:
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-3-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-ethyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-amino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-fluoro-1-azabicyclo[2.2.1]heptane;
5-[5-(3-methyl-1,2,4-oxadiazol)-yl]-3-methoxymethyl-1-azabicyclo[2.2.1]heptane;
5-[5-(3-methyl-1,2,4-oxadiazol)-yl]-3-methyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-hydroxymethyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-methoxy-1-azabicyclo[2.2.1]heptane;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-methyl-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-amino-1-azabicyclo[2.2.1]heptane;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-4-methyl-1-azabicyclo[2.2.1]heptane;
and salts and prodrugs thereof.

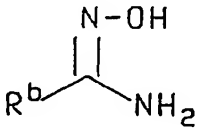
6. 3-[5-(3-Methyl-1,2,4-oxadiazol)-yl]-6-methyl-1-azabicyclo[2.2.1]heptane, and salts and prodrugs thereof.

7. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier.

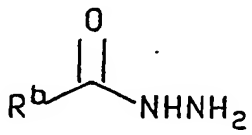
8. A pharmaceutical composition as claimed in claim 7 further comprising a peripheral cholinergic antagonist.

9. The use of a compound as claimed in any one of claims 1 to 6 for the preparation of a medicament for the treatment of neurological and mental disorders and/or for the treatment of severe pain.

10. A process for the preparation of a compound as claimed in any one of claims 1 to 6, which process comprises reacting a reactive derivative of a carboxylic acid of formula R^a-CO_2H with either a compound of formula IIIA or a compound of formula IIIB or a salt thereof:



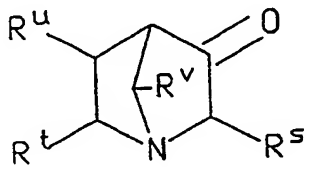
(IIIA)



(IIIB)

wherein one of R^a and R^b is a substituted 1-azabicyclo[2.2.1]heptane ring, and the other is a group of low lipophilicity.

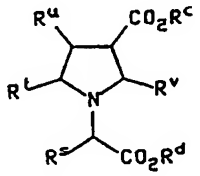
11. An intermediate of formula (V)



(V)

wherein R^s, R^t, R^u and R^v represent hydrogen, carboxylic acid ester, or a substituent R^3 or R^4 as defined in claim 1, or a group which is convertible thereto, at least one of R^s, R^t, R^u and R^v being other than hydrogen.

12. A process for the preparation of a compound as claimed in claim 11, which process comprises cyclising a compound of formula IV:

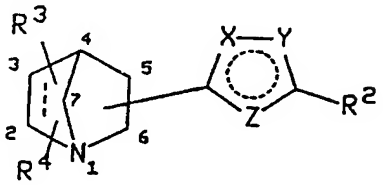


(IV)

wherein R^s, R^t R^u and R^v are as defined in claim 11, and R^c and R^d represent hydrocarbon groups.

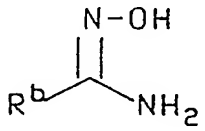
Claims for the following Contracting States: ES. GR

1. A process for the preparation of an oxadiazole represented by structural formula I:

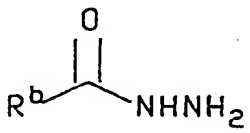


(I)

or a salt or prodrug thereof; wherein
one of X, Y or Z is an oxygen atom and the other two are nitrogen atoms, and the dotted circle represents aromaticity (two double bonds);
R^2 represents a substituent of low lipophilicity;
the broken line represents an optional chemical bond; and
the substituents R^3 and R^4 may be present at any position, including the point of attachment to the oxadiazole ring, and R^3 represents halo, C_{1-4} alkoxy, carboxy, $-NR^7R^8$, C_{2-4} alkyl, C_{1-4} alkyl substituted with hydroxy or C_{1-4} alkoxy, or methyl or hydroxy in the 3-, 4- or 5-position; and R^4 represents hydrogen, halo, C_{1-4} alkoxy, hydroxy, hydroxy, carboxy, $-NR^7R^8$, C_{1-4} alkyl, or C_{1-4} alkyl substituted with hydroxy or C_{1-4} alkoxy; or R^3 and R^4 together represent carbonyl; and
R^7 and R^8 independently represent hydrogen or C_{1-2} alkyl; which process comprises reacting a reactive derivative of a carboxylic acid of formula R^a-CO_2H with either a compound of formula IIIA or a compound of formula IIIB or a salt thereof:



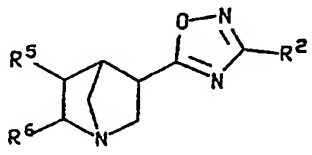
(IIIA)



(IIIB)

wherein one of R^a and R^b is a substituted 1-azabicyclo[2.2.1]heptane ring, and the other is a group of low lipophilicity.

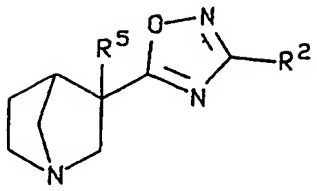
2. A process as claimed in claim 1 for the preparation of a compound represented by formula IIA:



(IIA)

wherein R^2 is as defined in claim 1, R^5 represents C_{1-4} alkyl, halo, $-NR^7R^8$, C_{1-4} alkoxy, hydroxy(C_{1-4})-alkyl, C_{1-4} alkoxy(C_{1-4})alkyl or hydroxy, and R^6 represents hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy.

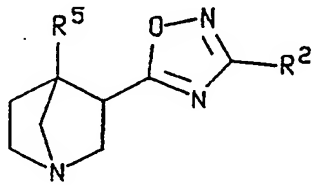
3. A process as claimed in claim 1 for the preparation of a compound represented by formula IIB:



(IIB)

wherein R^2 is as defined in claim 1 and R^5 is as defined in claim 2.

4. A process as claimed in claim 1 for the preparation of a compound represented by formula IIC:



(IIC)

wherein R^2 is as defined in claim 1 and R^5 is as defined in claim 2.

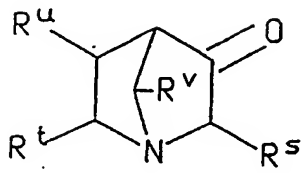
5. A process as claimed in claim 1 for the preparation of a compound selected from the following:
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-3-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-ethyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-amino-1,2,4-oxadiazol)-yl]-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-fluoro-1-azabicyclo[2.2.1]heptane;
5-[5-(3-methyl-1,2,4-oxadiazol)-yl]-3-methoxymethyl-1-azabicyclo[2.2.1]heptane;
5-[5-(3-methyl-1,2,4-oxadiazol)-yl]-3-methyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-5-hydroxymethyl-1-azabicyclo[2.2.1]heptane;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-1- azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-methoxy-1-azabicyclo[2.2.1]heptane;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-methyl-1-azabicyclo[2.2.1]heptan-5-ol;
3-[5-(3-dimethylamino-1,2,4-oxadiazol)-yl]-5-amino-1-azabicyclo[2.2.1]heptane;
3-[5-(3-methyl-1,2,4-oxadiazol)-yl]-4-methyl-1-azabicyclo[2.2.1]heptane;
and salts and prodrugs thereof.

6. A process for the preparation of a pharmaceutical composition which comprises mixing a compound prepared as claimed in any one of the preceding claims with a pharmaceutically acceptable carrier.

7. A process as claimed in claim 6 which further comprises incorporating a peripheral cholinergic antagonist into the composition.

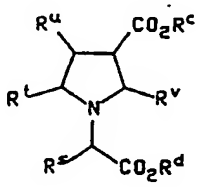
8. The use of a compound prepared as claimed in any one of claims 1 to 5 for the preparation of a medicament for the treatment of neurological and mental disorders and/or for the treatment of severe pain.

9. A process for the preparation of an intermediate of formula (V)



(V)

wherein R^s, R^t, R^u and R^v represent hydrogen, carboxylic acid ester, or a substituent R^3 or R^4 as defined in claim 1, or a group which is convertible thereto, at least one of R^s, R^t, R^u and R^v being other than hydrogen; which process comprises cyclising a compound of formula IV:



(IV)

wherein R^s, R^t, R^u and R^v are as defined above, and R^c and R^d represent hydrocarbon groups.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 88308125.9

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,P,X	EP - A2 - 0 239 309 (MERCK SHARP & DOHME LTD.) * Claims 1-3,5,7-10 * --	1-4,7-10	C 07 D 487/08 A 61 K 31/40// (C 07 D 487/08 C 07 D 209:00 C 07 D 209:00)
D,P,A	EP - A1 - 0 261 763 (BEECHAM GROUP PLC) * Claims 1,5,7,11,15 * --	1-4,7-9,12	
A	THE JOURNAL OF ORGANIC CHEMISTRY, vol. 34, 1969 D.O.SPRY et al. "Azabicyclic Alcohols. VI. Stereospecific Synthesis of the 1-Azabicyclo [2.2.1.] heptan-3-ol Epimers" pages 3674-3676 * Page 3675 * ----	11	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 487/00
C 07 D 453/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	16-12-1988	PETROUSEK

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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